International Immunopharmacology 141 (2024) 113006

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Review

Inflammation unleashed: The role of pyroptosis in chronic liver diseases

Lujian Zhu [a,1], Hongjie Tong [b,1], Chao Ren [c], Kun Chen [b], Shengnan Luo [a], Qin Wang [a], Maodong Guo [d], Yichen Xu [e], Minli Hu [d], Jinyong Fang [f], Jinxian Xu [a], Peifei Shi [b,*]

[a] Department of Infectious Diseases, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, China
[b] Department of Intensive Care Unit, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, China
[c] Department of Hepatobiliary and Pancreatic Surgery, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, China
[d] Department of Gastroenterology, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, China
[e] Department of Gerontology, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, China
[f] Department of Hematology, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, China

ARTICLE INFO

Editor: Yang Sun

Keywords:
Pyroptosis
NLRP3 Inflammasome
GSDMD
Caspase-1
Liver diseases

ABSTRACT

Pyroptosis, a newly identified form of programmed cell death intertwined with inflammatory responses, is facilitated by the Gasdermin family's pore-forming activity, leading to cell lysis and the release of pro-inflammatory cytokines. This process is a double-edged sword in innate immunity, offering protection against pathogens while risking excessive inflammation and tissue damage when dysregulated. Specifically, pyroptosis operates through two distinct signaling pathways, namely the Caspase-1 pathway and the Caspase-4/5/11 pathway. In the context of chronic liver diseases like fibrosis and cirrhosis, inflammation emerges as a central contributing factor to their pathogenesis. The identification of inflammation is characterized by the activation of innate immune cells and the secretion of pro-inflammatory cytokines such as IL-1α, IL-1β, and TNF-α.

This review explores the interrelationship between pyroptosis and the inflammasome, a protein complex located in liver cells that recognizes danger signals and initiates Caspase-1 activation, resulting in the secretion of IL-1β and IL-18. The article delves into the influence of the inflammasome and pyroptosis on various liver disorders, with a specific focus on their molecular and pathophysiological mechanisms. Additionally, the potential therapeutic implications of targeting pyroptosis for liver diseases are highlighted for future consideration.

1. Introduction

Programmed cell death is a fundamental biological process essential for the growth, development, and maintenance of homeostasis in multicellular organisms [1,2]. It encompasses six primary categories, including apoptosis, necrosis, pyroptosis, ferroptosis, autophagy, and efferocytosis [3]. Among these, pyroptosis, a new form of inflammatory cell death initiated by inflammatory stimuli, has emerged as a critical area of study, yet its mechanisms are not fully understood and warrant further scrutiny [4,5].

Pyroptosis is characterized by the secretion of pro-inflammatory cytokines, which are integral to the innate immune response against both infectious and noninfectious stimuli [6,7]. As a fundamental component of the innate immune system, it is integral in safeguarding the body against pathogenic microorganisms and external stressors through the activation of Caspase-1 and the subsequent release of inflammatory cytokines such as IL-1β and IL-18 [8–10]. Besides, the inflammatory vesicle plays a pivotal role in the process of pyroptosis, facilitating communication between the immune system and cells. The activation of inflammatory vesicles has been implicated in various pathological conditions, including metabolic fatty liver disease, liver fibrosis, gout, heart disease, diabetes, and Alzheimer's disease, underscoring the necessity for precise regulation [11–14]. USP3 has been recognized as a key regulator of apoptosis-associated speck-like protein containing CARD domain (ASC) ubiquitination, maintaining the proper functioning of ASC-mediated inflammatory vesicle activation and suggesting a novel pathway by which ASC ubiquitination regulates inflammatory vesicle activation [15]. Additionally, inflammatory vesicles play a critical role in the host's response to pathogens. For instance, the activation of the inflammasome is vital for the host's innate immune response upon pathogen invasion [16]. Caspase-1, a crucial component of the inflammasome, has a beneficial impact on various pathogen

* Corresponding author.
E-mail address: shipfff@163.com (P. Shi).
[1] The first two authors contributed equally to this work.

https://doi.org/10.1016/j.intimp.2024.113006
Received 12 June 2024; Received in revised form 4 August 2024; Accepted 20 August 2024
Available online 29 August 2024
1567-5769/© 2024 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC license (http://creativecommons.org/licenses/by-nc/4.0/).

incursions [17,18]. Moreover, numerous research studies have identified the role of Caspase-11 in unconventional inflammatory vesicles in pyroptosis and the release of specific inflammatory mediators [19]. This indicates that inflammatory vesicles are not solely linked to intracellular signaling and regulation, but also play a crucial role in the cellular response to external stimuli.

While our understanding of pyroptosis has grown, there is a need for a critical appraisal of the existing literature to assess the validity and implications of the published data. This includes evaluating the conceptual and methodological rigor of primary studies, which is essential for advancing scientific knowledge and developing robust treatment strategies. Several previous studies have underscored the key points of pharmaceutical research, ranging from drug solubility and formulation to the exploration of natural products for therapeutic applications and the development of analytical techniques for quality control [20–23], the above literature may shed light on the further studies about treatment strategy based on pyroptosis regulation. Here, this review delves into the progression of inflammasome and pyroptosis and their impact on various liver conditions, we hope that a thorough analysis of the inflammasome and pyroptosis will offer new perspectives for clinical practice, contributing to the development of more effective therapies for patients suffering from chronic liver conditions.

2. Molecular mechanisms of pyroptosis

Pyroptosis is a physiological process in animals that serves multiple functions including growth, homeostasis maintenance, and aging. It is characterized by programmed cell death initiated by inflammatory caspases, acting as a defense mechanism against external pathogens [24,25]. However, excessive pyroptosis can result in inflammatory responses and immune system dysregulation [26–28]. Pyroptosis is commonly induced by intracellular pathogen invasion, leading to Caspase-1-dependent pyroptosis in monocytes, macrophages, and dendritic cells infected with diverse microbial pathogens [29–31]. Furthermore, various damage-associated molecular patterns (DAMPs) can also induce pyroptosis in cells other than macrophages [32]. Before we can understand the mechanisms of pyroptosis, we need to recognize two important components: inflammatory vesicles and Gasdermin D (GSDMD).

2.1. Inflammasome

The term “inflammasome” was first introduced by Tschopp et al. (2002) [33] to describe a collection of large multiprotein complexes that detect endogenous danger signals through the NOD-like receptor (NLR), a member of the pattern-recognition receptor family characterized by a C-terminal leucine-rich repeat (LRR) domain for ligand recognition, a central NACHT domain for oligomerization and dNTPase activation, and an N-terminal domain for the same functions. The protein contains a central NACHT domain, which is involved in recognizing ligands, as well as a structural region at the N-terminal responsible for oligomerization and dNTPase activation [34–38]. Among them, scholars have classified the protein complex into three subgroups according to the NACHT structural domains: (1) NOD (NOD1-5, CIITA); (2) NLRP or NALP (NLRP/NALP1-14); (3) IPAF (IPAF, NAIP) [39,40]. There are also several other classifications based on N-terminal effector domains. Not all NLRs are involved in inflammasome formation. Except for AIM2, the inflammasome is named according to the NLR [41,42].

The inflammasome is composed of the sensor NLR and the effector pro-caspase-1, with some inflammasomes additionally incorporating linker proteins, such as ASC [38,43,44]. Activation of the inflammasome leads to the cleavage of the inactive caspase-1 precursor into the p20 and p10 subunits, resulting in the formation of active caspase-1. This cascade ultimately leads to the processing and secretion of pro-IL-1β and pro-IL-18, along with the inactivation of IL-33 [43,45,46]. IL-1β, a cytokine known for its pro-inflammatory properties, functions by interacting with the IL-1 receptor (IL-1R) and is commonly referred to as IL-1R. This interaction leads to the generation of diverse biological responses [47]. Additionally, IL-1R has the ability to recognize IL-1α and bind to the IL-1R antagonist (IL-1Rα), thereby inhibiting IL-1R activation [48]. Furthermore, IL-18 induces NK cells to release IFN-γ, while IL-33, a member of the IL-1 family, is associated with chromatin and promotes the Th2 immune response [49,50]. IL-33, a cytokine belonging to the IL-1 family, is associated with chromatin and promotes the Th2 immune response. Caspase-1 cleaves and deactivates active IL-33 [51].

The inflammasome is activated through a two-step process: the first step involves an increase in inflammasome expression, primarily due to TLR activation, while the second step involves the activation of a functional inflammasome by inflammasome ligands [52]. It has been recently shown that initiation of step one only requires activation of NLRP3, but not other Inflammasome ligands including PAMPs and DAMPs [53–56]. Currently, there have been four primary models of the inflammasome recognized: NLRP1 (NALP1); NLRP3 (NALP3); NLRC4 (IPAF); and AIM2 [57]. Each of them possesses unique ligand recognition sites and adapter molecules, yet they all lead to the activation of the caspase. Despite variations in ligand recognition sites and adapter molecules, all pathways lead to the activation of caspase-1 and result in an inflammatory response [57,58].

2.1.1. NLRP1 inflammasome

The first identified inflammasome, NLRP1, is a complex made up of multiple proteins with NACHT, LRR, and PYD domains that interact with cysteine-aspartase-1 through its CARD domain. The complex’s activity is boosted by the presence of ASC [59,60]. NLRP1 is a crucial component of the human immune system, detecting various internal threats like cellular harm and infections, and triggering an inflammatory reaction [61]. Furthermore, there are numerous alternative splicing variants for the human NLRP1 gene, which can be triggered by cytosolic acyl dipeptides and lethal toxins from Bacillus anthracis [62]. NLRP1 and NOD2 proteins must interact for the activation and release of IL-1β to occur [63]. Activation of NLRP1 can also be triggered by cytosolic acyl dipeptides and the lethal toxin produced by Bacillus anthracis.

The efflux of potassium ions is intricately associated with the activation of the NLRP1 inflammasome, a molecular complex responsible for sensing changes in the intracellular milieu and responsive to diverse stimuli, including fluctuations in intracellular potassium ion concentrations. The reduction in intracellular potassium levels resulting from potassium ion efflux can induce the activation of the NLRP1 inflammasome, with the decrease in intracellular potassium ion concentration serving as a critical signal for this process [64]. Activation of the NLRP1 inflammasome leads to the enhancement of pro-inflammatory cytokines (e.g., IL-1β and IL-18), which play a crucial role in initiating and controlling inflammatory reactions [65].

2.1.2. NLRP3 inflammasome

The NLRP3 inflammasome plays a crucial role in the human immune system, mainly contributing to inflammation and pyroptosis [66]. The NLRP3 inflammasome is a complex made up of NLRP3 proteins, ASC, and caspase-1 precursor, interacting to form the complex initially identified by Hoffman et al. [55].

Because NLRP3 lacks a CARD structural domain, the existence of an ASC is crucial for complex formation. Activation of the NLRP3 inflammasome usually requires multiple signals to be induced, including PAMPs, DAMPs, and environmental factors such as temperature changes or toxins (Fig. 1) [67]. NF-κB tightly regulates the transcriptional expression of NLRP3. Stimulation of cells with NF-κB activators (e.g., lipopolysaccharides, a ligand for TLR4) is NLRP3 is the first step [68], followed by the induced activation of the above signals. These signals activate the NLRP3 protein, which further contributes to the assembly of the inflammasome.

The activation of the NLRP3 inflammasome involves multiple mechanisms that can be categorized into three main pathways:

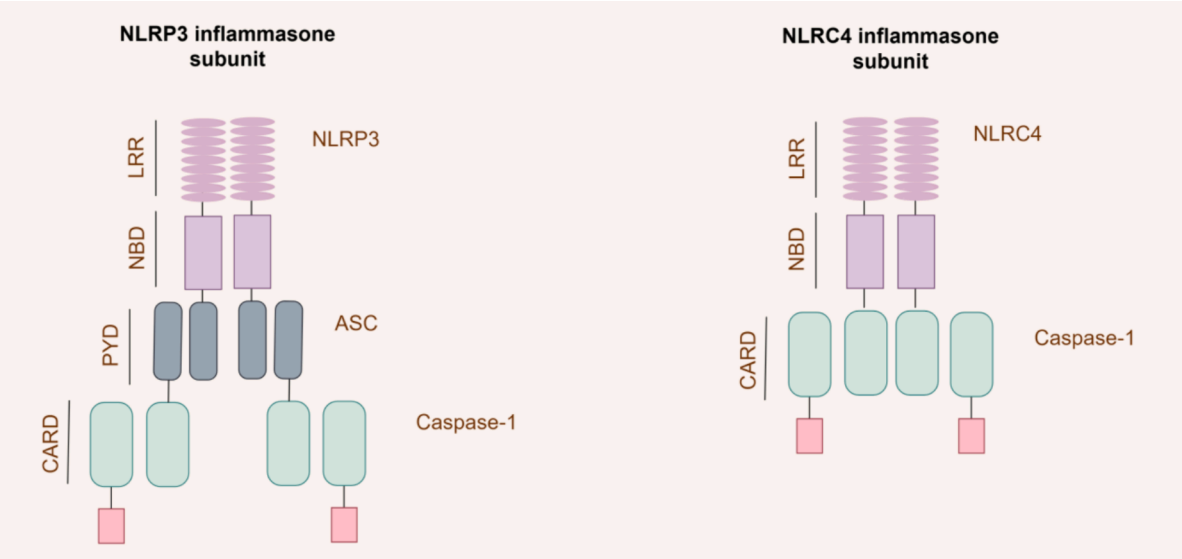

Fig. 1. Monomer structures of NLRP3 and NLRC4 inflammasome subunit. LRP: leucine-rich repeat sequence; NBD: nucleotide-binding and oligomerisation structural domain; PYD: thermoprotein structural domain; CARD: caspase activation and recruitment domain structural domain CARD.

potassium ion release, reactive oxygen species (ROS) generation, and lysosomal damage resulting in rupture. In the initial pathway, exposure of the cell to a particular stimulus, such as a bacterial toxin or ATP, leads to activation of the P2X7 purinergic receptor, which in turn triggers the opening of potassium channels on the cell membrane, resulting in the efflux of intracellular potassium and the mobilization of ubiquitylated connexins. After this process, NLRP3 is activated, leading to the creation of a membrane pore facilitating the ingress of extracellular PAMPs and DAMPs into the cytosol. A reduction in potassium ion levels serves as a pivotal stimulus for the activation of the NLRP3 inflammasome, albeit the precise mechanism of activation remains incompletely elucidated [69]. In the alternative pathway, lysosomes, which are intracellular organelles responsible for the degradation of substances from internal and external cellular origins, play a significant role. Cells can take in significant quantities or sizes of particulate matter (e.g. uric acid crystals, cholesterol crystals, asbestos fibres, etc.), this can lead to damage and rupture of the lysosome [70]. Upon lysosomal rupture, the release of enzymes and other substances can trigger the activation of the NLRP3 inflammasome either through direct or indirect means. Additionally, the activation of NLRP3 can also be induced by ROS, a group of chemicals including peroxides and free radicals that are produced during cellular metabolism. While ROS serves as important signaling molecules at low concentrations, excessive levels can be detrimental [71]. Various stimuli, such as infection or cellular stress, can result in the overproduction of ROS. Elevations in ROS can trigger the activation of the NLRP3 inflammasome, making it a crucial factor in its activation. Reducing ROS production or NADPH oxidase inhibitors or scavengers (which remove produced ROS) can inhibit NLRP3 activation [72]. ROS are generated by different cellular insults and can be induced by large particulate molecules capable of activating the inflammasome, as well as by ATP [73,74]. However, ROS production does not necessarily lead to NLRP3 activation.

2.1.3. NLR family CARD structural domain protein 4 (NLRC4) inflammasome

The NLRC4 inflammasome, a protein complex consisting of NLRC4/IPAF (Fig. 1), plays a crucial role in triggering the inflammatory response in cells in reaction to various stress conditions, including infections [75]. Activation of the NLRC4 inflammasome can be induced by flagellin from both Gram-positive and Gram-negative bacteria, as well as by the type III secretion system (T3SS) of Gram-negative bacteria [76,77]. Despite its importance, the precise mechanisms of activation of the NLRC4 inflammasome remain unclear. NLRC4 serves as a key component of this complex, responsible for detecting pathogens and initiating immune responses [76]. Simultaneously, NLRC4 inflammasome activation triggers caspase-1 enzyme activation, facilitating the development and release of vital inflammatory cytokines like IL-1β and IL-18 to combat infections and uphold immune balance [78]. However, aberrant activation of the NLRC4 inflammasome may also contribute to inflammatory diseases [76].

2.1.4. Absent in melanoma 2 (AIM2) inflammasome

The AIM2 inflammasome, a critical intracellular protein complex, plays a vital role in immune system functionality. Activation of this inflammasome occurs in response to bacterial, viral, and mammalian host DNA within the cytoplasm, particularly in the presence of double-stranded DNA [79]. AIM2, a member of the Pattern Recognition Receptors (PRRs), is a fundamental part of the inflammasome. AIM2, a key element of the inflammasome, is part of the PRRs category, which identifies PAMPs and DAMPs [80].

Upon detection of double-stranded DNA by AIM2, whether from pathogens or intracellular damage, AIM2 becomes active and interacts with ASC and caspase-1 to create the AIM2 inflammasome [81]. This assembly triggers caspase-1 activation, resulting in the production and release of IL-1β and IL-18 [82]. These cytokines are key mediators of the inflammatory response, helping to protect against infection and maintain immune homeostasis. However, overactivation or dysfunction of the AIM2 inflammasome may also contribute to autoimmune and inflammation-related diseases.

2.2. Gasdermin D (GSDMD)

GSDMD plays a crucial role in the pyroptosis pathway by acting as a direct substrate for Caspase-1/4/5/11 during pyroptogenesis [83]. Activation of GSDMD leads to the initiation of pyroptosis, a process that requires the involvement of multiple Caspases, including Caspase-1, 4, 5, and 11 [84]. Cleavage of GSDMD by Caspase-1/4/5/11 generates GSDMD-NT, which serves as a trigger for pyroptosis. GSDMD-NT binds to inner membrane components and forms a pore with a diameter ranging from 10 to 33 nM [85,86]. GSDMD-NT can also stimulate the NLRP3-mediated initiation of the caspase-1 inflammasome, potentially involving the creation of a pore triggered by GSDMD leading to the release of potassium ions.

2.3. The two main molecular mechanisms of pyroptosis

Pyroptosis involves two primary molecular pathways: the classical pathway, which is dependent on Caspase-1, and the non-Caspase-1-dependent pathway. Both pathways result in the release of pro-inflammatory cytokines IL-1β and IL-18 (Fig. 2), amplifying local or systemic inflammation [87].

2.3.1. Classical inflammasome-induced pyroptosis pathway

The classical pathway of pyroptosis is pyroptosis induced by inflammasome known as cytoplasmic multiprotein complex. Up to this point, researchers have discovered four different types of inflammasomes, which are NLRP1, NLRC4, AIM2, and NLRP3 [55]. The inflamed vesicles can detect different triggers that lead to pyroptosis. NLRP3, a well-researched inflammasome, can be triggered by various microbial and host-derived stimuli such as bacteria, viruses, humidity, pore-forming toxins, and more. The pyrophosphatase process is highly preserved across various cell types and has been demonstrated to require the activation of both conventional caspase-1 and non-traditional caspase-4/5/11 (human caspase-4/5 and mouse caspase-11) [88,89]. NLRs (NLRP3, NLRP1, NLRC4, NLRP9, and NLRP6) trigger the activation of PAMP or DAMP through the pyrochain reaction signaling pathway, PYHIN, a group of purinergic proteins not found in AIM 2, along with pyrimidine proteins [90,91]. The activated inflammasomes trigger caspase-1 activation, resulting in pyroptosis. NLR proteins consist of LRR, NOD/NACHT, CARD, or PYD. LRR is required for ligand recognition and autoimmunity. The NOD/NACHT structural domain plays a key role in activating ATP-dependent signalling complexes [92].

2.3.2. Non-classical inflammasome-induced pyroptosis pathway

The activation of the noncanonical inflammasome pathway is dependent on caspase 4/5/11 rather than caspase-1 [93]. Caspase-11 is predominantly expressed in mice, while caspase-4/5 is found in humans [94]. These proteins have the ability to directly recognize lipopolysaccharides (LPS) from Gram-negative bacteria, leading to pyroptosis as the primary response upon their activation. In the context of non-classical pyroptosis, the CARD domain of caspase-4/5/11 interacts with LPS, resulting in its aggregation and subsequent activation, thereby initiating protease activity. The active caspase-4/5/11 then cuts GSDMD into GSDMD-NT, creating pores in cell membranes with sizes between 10–15 nm, triggering the start of pyroptosis [95]. GSDMD-NT induces caspase-1-dependent activation of the NLRP3 inflammasome, leading to the secretion of IL-1β and IL-18, which may be associated with the augmentation of conventional thermoregulatory mechanisms [96]. Pyroptosis is implicated in the production of IL-1β and IL-18, contributing to the initiation and perpetuation of acute and chronic inflammatory responses. Furthermore, pyroptosis serves as an endogenous pyrogen, promoting the onset of fever.

3. Role of pyroptosis in liver diseases

The increasing incidence of liver disease presents a substantial worldwide public health concern over a prolonged duration, resulting in the onset of cirrhosis and liver cancer in certain individuals due to various factors [97]. Recent studies suggest that pyroptosis effectively removes infected cells, with emerging evidence highlighting its potential role in the advancement of liver ailments [98]. Hepatic inflammation, infectious liver fibrosis, and hepatocellular carcinoma have been shown to be associated with pyroptosis during the progression of cirrhosis [99–101].

3.1. Pyroptosis and viral hepatitis

Viral hepatitis, a liver inflammation resulting from viral infection of liver cells, is associated with a high death rate. Hepatitis B virus (HBV) and Hepatitis C virus (HCV) are frequently encountered and have the potential to lead to liver fibrosis, cirrhosis, and hepatocellular carcinoma [102]. LPS has the potential to strongly stimulate pyroptosis in

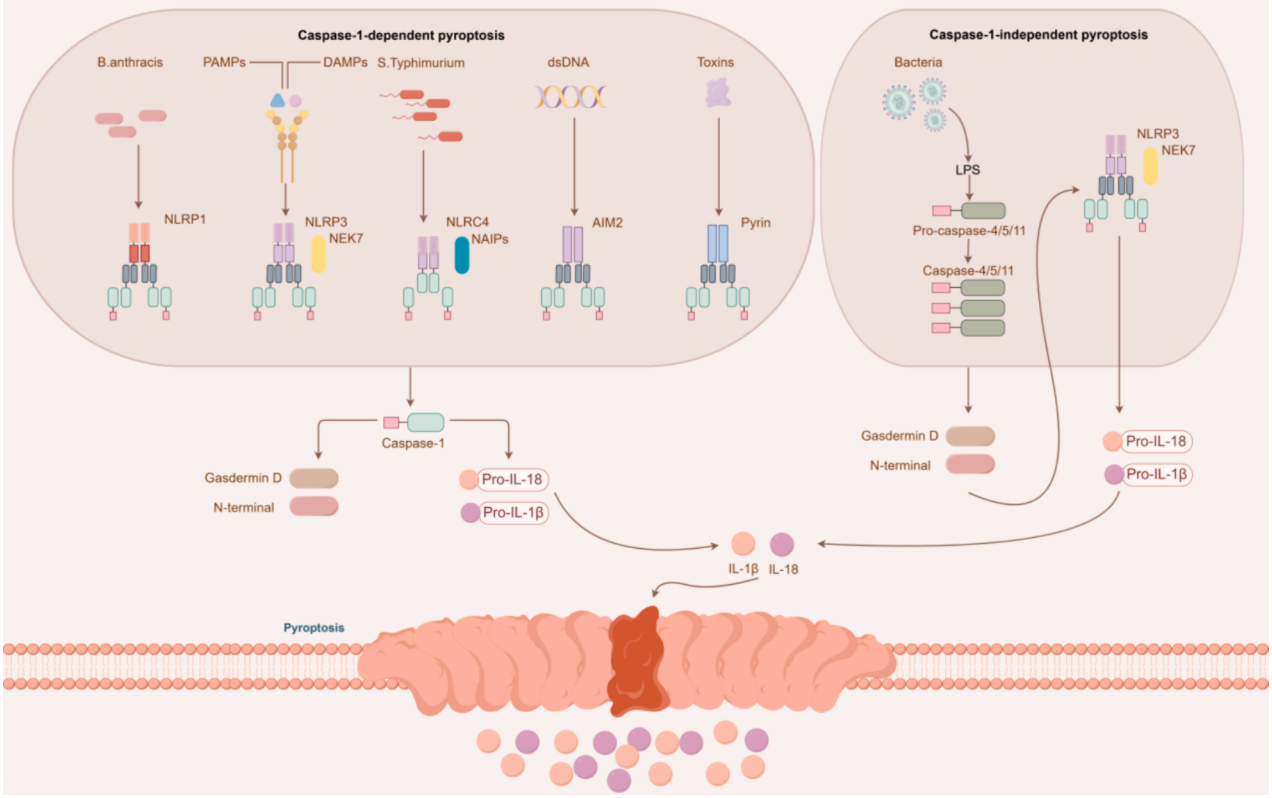

Fig. 2. Two main molecular mechanisms of pyroptosis: classical caspase-1-dependent and non-caspase-1-dependent pathways.

liver cells, leading to the activation of pyroptosis and impacting the development of liver conditions [103]. Research has shown that pyroptosis is linked to the development and advancement of hepatitis B and C among viral hepatitis [94]. Activation of inflammatory vesicles and induction of pyroptosis are triggered by the detection of viral DNA/RNA and PRRs [104]. During various viral infections, the TM structural domain of the transfer receptor inhibits the activation of pyroptosis markers such as cleaved caspase-1 and IL-1β by disrupting AIM2-dependent signaling pathways [105]. The presence of the Hepatitis B virus hinders the activation of NLRP3 and IL-1β caused by lipopolysaccharide by blocking the NF-κB signaling pathway and the production of reactive oxygen species [106]. Moreover, studies have shown that hepatitis B core antigen (HBcAg) can stimulate the release of IL-18, which is another indicator of pyroptosis. This suggests that the invasion of HBcAg is a significant factor in triggering HBV-induced pyroptosis [107]. In conditions where hydrogen peroxide is present, the NLRP3 inflammasome is triggered by elevated levels of mitoROS, leading to the initiation of hepatic inflammation and pyroptosis induced by the Hepatitis B virus x protein (HBx) [108,109]. The Hepatitis C virus has the ability to trigger pyroptosis through the activation of caspase-1 and caspase-3 pathways [110]. In liver cells, the creation of lipid droplets is strongly linked to NLRP3, resulting in changes in shape and the multiplication of HCV, which contributes to the progression of liver disease [111]. Studies have shown that in cases of chronic HCV, Kupffer cells produce IL-1β, which is linked to inflammation and is a significant contributor to IL-1β levels [112].

3.2. Pyroptosis and alcoholic liver disease (ALD)

ALD is a global disease with a high death rate caused by liver inflammation from excessive drinking of alcohol. Although the molecular mechanisms of ALD are unknown, there are no effective therapeutic strategies. Nevertheless, frequent alcohol intake is frequently linked to numerous instances of cell demise, such as pyroptosis [113]. Caspase-11/4 activation triggers GSDMD, leading to pyroptosis via the caspase-11/4-GSDMD signaling pathway, potentially influencing the development of ALD [114,115]. Extensive evidence indicates that the gut microbiome, heightened intestinal permeability, and endotoxin are crucial factors in the progression of ALD [116]. Elevated levels of IL-1β in the serum have been observed in both alcoholics and animal models of liver disease caused by alcohol consumption [117,118]. Hsiang et al. Exposed HepG2 cells to acetaldehyde, a byproduct of alcohol, resulting in the secretion of IL-1β and TNF-α [119]. Research has demonstrated that in a mouse model with chronic alcohol consumption, there is an increase in mature IL-1β levels in the blood and liver, higher activation of hemi-caspase-1, and upregulation of NLRP3 inflammasome, ASC, and pro-caspase-1 in the liver. This indicates that the activation of inflammasomes and pyroptosis play a role in the development of ALD [120]. Interestingly, caspase-1, a key component of the pyroptosis pathway, remained unchanged in the ALD mouse model, suggesting the need for additional research. Moreover, NLRP3 has the ability to attract ASC and pro-caspase-1 in order to activate caspase-1, leading to liver damage [121]. The activation of inflammatory vesicles by NLRP3 is strongly linked to ROS, with mitochondria being the primary source. Numerous research studies have validated the importance of mitochondria-linked energy metabolism, signal transduction, and ROS generation in the process of programmed cell death [122].

3.3. Pyroptosis and metabolism-associated fatty liver disease (MAFLD)

MAFLD, previously known as non-alcoholic fatty liver disease (NAFLD), is a common chronic liver disease, a condition in which fat accumulates in liver tissue even in the absence of heavy alcohol consumption or associated metabolic disorders. Including everything from simple hepatic steatosis to metabolism-associated steatohepatitis (MASH) and even cirrhosis, these classifications are based on the degree of inflammatory damage present in the liver cells. Currently, MAFLD poses a major challenge. The most recent data indicate that its incidence is on the rise globally, reaching 24 %, and that it poses a considerable economic burden [123]. The increasing prevalence and high risk of MAFLD progressing to cirrhosis and hepatocellular carcinoma have made it a significant health concern. The importance of pyroptosis in the pathogenesis of MAFLD has been increasingly recognized as research into liver disease has intensified. Recent research has indicated that pyroptosis is a significant factor in the development of MAFLD into MASH, contributing to lipid accumulation and oxidative stress that ultimately causes damage to liver cells [124]. Liu [125] demonstrated that excessive buildup of phospholipids within the liver increases the levels of NLRP3 inflammasome, ASC, and caspase-1, leading to the activation of pyroptosis and worsening liver damage in MASH. Furthermore, research was conducted using HepG2 cells to create MASH models, revealing a notable rise in the levels of NLRP3, GSDMD, and IL-1β in the model group. This indicates that the NLRP3 inflammasome plays a role in the development of MASH [126]. Insulin resistance plays a key role in the development of MAFLD by activating NLRP3, which in turn triggers inflammatory factors like IL-1β, IL-18, and NF-κB. These factors are strongly linked to insulin resistance and contribute to the progression of MAFLD [127]. It has also been shown that NLRP3inflammasome induces Caspase-1 cleavage in hepatocytes after sensing lipotoxicity-associated ceramides, which ultimately leads to the pyroptosis of the MAFL temporal phase [128]. Thus, activation of NLRP3 vesicles is critical for pyroptosis, which leads to MAFLD with MASH.

3.4. Pyroptosis and liver fibrosis

Liver fibrosis is the excessive deposition of extracellular matrix in liver tissue, leading to structural and functional changes in the liver. Underlying these changes is an imbalance between fibrogenesis and fibrinolysis caused by chronic liver injury. Activation of the NLRP3 inflammasome can lead to pyroptosis in both mouse and human liver cells, resulting in the release of NLRP3 inflammasome and contributing to the development of fibrosis driven by inflammasome [7]. The primary components of liver cells include hepatocytes, hepatic stellate cells (HSC), bile duct epithelial cells, natural killer cells, and Kupffer cells [129]. Research has demonstrated that hematopoietic stem cells can become more active when exposed to signaling molecules released by Kupffer cells or other inflammatory cells [130]. When NLRP3 is triggered, it can activate HSC, leading to the release of IL-1β and IL-18, which in turn causes hepatocytes to experience pyroptosis. Additionally, NLRP3 can promote tissue fibrosis [131]. Recent studies have shown that extracellular ATP can trigger the NLRP3 inflammasome in HSC through the purinergic receptor P2X7 in vitro tests, resulting in the secretion of fibrosis indicators like α-SMA and collagen type I, ultimately causing liver fibrosis. Additionally, the ATP-dependent purinergic 2X7 receptor (P2X7R) is crucial in hepatic inflammation during the progression of liver fibrosis [132]. Activation of the P2X7R-NLRP3 axis by bacterial LPS/ATP signaling triggers the release of IL-1β from HSC, potentially leading to ECM secretion and deposition, indicating that targeting this pathway could be a promising therapeutic approach for liver fibrosis [133].

3.5. Pyroptosis and primary liver cancer (PLC)

PLC is a malignant tumour arising from hepatocytes or intrahepatic biliary epithelial cells and is mainly classified into hepatocellular carcinoma (HCC), cholangiocarinoma and mixed histopathological types of hepatocellular carcinoma. Pyroptosis is a cell death pathway that causes inflammation from within, discovered recently as pro-inflammatory, known for cytolysis and the release of inflammatory cellular contents [134]. Caspase-1 activation enhances the release of inflammatory cytokines, potentially resulting in cancer or programmed cell death. Induction of pyroptosis was found to have an inhibitory effect on primary

hepatocellular carcinoma [135]. Wei et al. [136] examined the presence of NLRP3 inflammasome elements in tissues from 128 patients with liver cancer and adjacent tissues using immunohistochemistry. The findings indicated positive expression of Caspase-1, NLRP3, ASC, and IL-1β, indicating the occurrence of pyroptosis. Furthermore, the NLRP3 expression level in tissues of hepatocellular carcinoma was inversely associated with both its pathological grade and clinical stage, indicating a potential role of pyroptosis in suppressing the progression of hepatocellular carcinoma. Another study revealed a significant decrease in the expression of the NLRP3 inflammasome component, which was implicated in the advancement of hepatocellular carcinoma [137]. In addition, Lin et al. [138] in this study, researchers discovered that levels of interferon-inducible nuclear protein 16 (IFI16) were lower in hepatocellular carcinoma tissues compared to normal tissues. The increased expression of IFI16 led to a decrease in cell viability, resulting in a significant inhibition of tumour growth and reduction in tumour size. Additionally, the overexpression of IFI16 activated the inflammasome through caspase-1, leading to the cleavage of IL-1β precursor (pro-IL-1β)/IL-18 and an increase in IL-1β and IL-18 levels. It was observed that the tumour-suppressing effect of IFI16 could be effectively blocked by a caspase-1 inhibitor, suggesting a potential link between IFI16-mediated tumour suppression and caspase-1-induced pyroptosis. With the increasing research on pyroptosis, the mechanism of pyroptosis in the precancerous lesions of primary hepatocellular carcinoma and in the disease progression of primary hepatocellular carcinoma has been gradually elucidated.

3.6. Pyroptosis and hepatic Ischemia-Reperfusion injury (HIRI)

HIRI is a common clinical complication that often occurs after hepatic lobectomy, hypovolemic shock due to hepatic portal blockade and other factors in liver transplantation, resulting in local and distal cellular damage and organ dysfunction [139]. The primary characteristics of HIRI include hepatocyte demise, release of PAMP and DAMP, infiltration of various inflammatory cells, activation of Kupffer cells, production of ROS, and damage to hepatic sinusoidal endothelial cells (LSECs), potentially resulting in inflammasome activation. Studies have demonstrated that the activation of Kupffer cells is crucial in the onset of HIRI, as it is initiated by the release of inflammatory factors that create the essential environment for initiating the pyroptosis pathway in HIRI [140]. The strongest known activator of Kupffer cells is LPS [141]. HIRI is currently divided into two phases, with phase I injury being predominantly mediated by Kupffer cells and phase II injury being predominantly mediated by neutrophils. Phase I injury refers to the acute damage to liver cells due to the release of high levels of reactive oxygen species and inflammatory factors from activated Kupffer cells. Phase II injury is a result of phase I injury, triggered by the activation and release of inflammatory factors that activate the inflammatory response pathway. This leads to a significant accumulation and adhesion of activated neutrophils in the liver, causing damage through the release of oxygen-free radicals and proteases. Additionally, hepatic sinusoidal stenosis can block hepatic sinusoids, worsening hepatic microcirculation and resulting in liver cell damage and impaired liver function [142]. No specific drug against pyroptosis has been found, therefore, it has become a hotspot of current research to prevent the transformation to phase II injury by inhibiting Kupffer cells or suppressing the inflammatory factors released by them. Additionally, blocking the NLRP3 inflammasome has been shown to improve liver cell damage caused by ischemia/reperfusion and decrease the secretion of IL-1β, IL-18, Hepatocytes release high mobility group box 1 (HMGB1), IL-6, and TNF-α by suppressing the Caspase-1 and NF-κB pathways [143]. N-acetylcysteine significantly decreased caspase-1 activity during liver injury caused by ischemia/reperfusion [144]. During the reoxygenation phase, caspase-1 and apoptosis were observed, which differed from the mainly necrotic characteristics of the hypoxic phase. During both the hypoxic and reoxidative phases, caspase-1 was detected, and the use of specific caspase-1 inhibitors like YVAD effectively blocked cell death caused by I/R [145]. In summary, the process of HIRI causes pyroptosis through the activation of inflammatory factors, which act as a bridge linking hepatic ischemia–reperfusion to pyroptosis, and if their activation can be inhibited, this pathway of pyroptosis can undoubtedly be blocked, thus attenuating HIRI.

3.7. Pyroptosis and autoimmune hepatitis (AIH)

AIH is a long-lasting condition where the immune system of the body targets the regular structure and operation of the liver, causing swelling and harm to the liver. Prior research has indicated that AIH includes the stimulation of T cells (in a manner not dependent on T cell receptors) and natural killer T (NKT) cells through cytokines [146]. In AIH mouse models, NKT cells show expression of the OX40 co-stimulatory molecule and elevated levels of caspase-1 [147]. OX40 decreases the suppressive function of T cells (Tregs), leading to increased T cell activation. Activation of Caspase-1 results in the maturation and release of IL-1β and GSDMD-mediated pyroptosis [148]. Studies have demonstrated that caspase-1-mediated pyroptosis is also present in ConA-induced liver injury (a model of AIH) [149]. Additionally, as previously stated, GSDMD acts as the executor in the pyroptosis process by serving as a target for caspase-1 and caspase-11, both essential for facilitating pyroptosis [150]. After ConA stimulation, the absence of GSDMD results in increased inflammation in the portal and lobular areas, larger regions of hepatic necrosis, elevated levels of serum aminotransferases, and greater hepatocyte apoptosis [151]. Pyroptosis, a type of inflammatory cell death, is primarily identified by the creation of pores in the cellular membrane. During an autoimmune disorder-related antigen–antibody reaction, the pattern recognition receptor binds to the precursor of Caspase-1 through ASC. This leads to the activation of Caspase-1 by the NLRP3 inflammasome, a member of the NLRs family. The activated Caspase-1 then cleaves GSDMD, producing peptides with nitrogen-terminal active domains. These peptides trigger the maturation and release of the inflammatory cytokines IL-1β and IL-18, enhancing the inflammatory response, initiating an innate immune response, and inducing pyroptosis [152]. The excessive inflammation caused by programmed cell death disrupts the immune system's equilibrium, leading to increased inflammation and cytokine production in AIH. This worsens the inflammatory response and liver damage, playing a crucial role in the progression of the disease.

3.8. Pyroptosis and sepsis-associated liver injury

Sepsis is a serious condition caused by the body's immune response not functioning properly, leading to organ dysfunction that can be life-threatening. Sepsis is commonly linked to the production of multiple pro-inflammatory cytokines, a phenomenon frequently known as a 'cytokine storm' [153]. The liver, being the largest glandular organ in the body, has a high blood flow and plays a role in regulating metabolic and immune balance, yet it is frequently impacted in cases of sepsis. Research has demonstrated that pyroptosis is crucial in controlling the progression and outcome of sepsis [154]. Moderate activation of pyroptosis helps to clear infected cells promptly, but an overly strong response can result in massive cell death, organ damage, and even failure. During sepsis-related liver damage, the liver plays a crucial role in protecting against the invasion of pathogens into the bloodstream. Recent studies have demonstrated a notable increase in pyroptosis pathway-related proteins in individuals with sepsis-induced acute liver damage. Conversely, mice lacking GSDMD exhibit decreased liver injury and markedly enhanced survival rates [155]. Meanwhile, the animal infection model provides a basis for studying the role of hepatic pyroptosis pathway in septic liver injury. Cecum ligation puncture (CLP) has become the accepted method for creating the mouse sepsis model, known as the standard model for polymicrobial sepsis. In the mouse model of sepsis induced by CLP, the levels of Caspase-1 and NLRP3

proteins related to hepatic pyroptosis were elevated and showed a positive relationship with the severity of liver damage. However, pretreatment with NLRP3 or Caspase-1 inhibitors in vitro significantly decreased the harm inflicted on hepatocytes by LPS [156]. Besides the traditional route, infected hepatocytes can also facilitate cellular connections, helping LPS trigger caspase-11 in macrophages and endothelial cells through an alternative pathway. HMGB1 can attach to LPS outside the cell and then be taken into lysosomes in macrophages or endothelial cells through the receptor for advanced glycation end-products (RAGE) [157]. HMGB1 breaks down the phospholipid layer of lysosomes, aiding in the liberation of LPS into the cytosol for the activation of caspase-11 and subsequent pyroptosis [158].

4. Implications of targeted pyroptosis in the treatment of liver disease

Recent research has demonstrated the significant impact of pyroptosis on the advancement of liver conditions, indicating that focusing on pyroptosis could be a beneficial approach to liver disease management. At present, there exist two primary approaches to prevent pyroptosis. An approach to suppress the NLRP3 inflammasome is by utilizing regulatory pathways, such as MCC950, which is recognized as an NLRP3 inhibitor. This compound has been shown to significantly reduce cholestatic liver damage and inflammation in a mouse model of bile duct ligation (BDL). Research has demonstrated that MCC950 effectively reduces liver damage caused by blood stasis syndrome by decreasing the levels of inflammatory cytokines like IL-1β and IL-18, as well as preventing neutrophil infiltration and hepatocyte death [159]. Interferon-1 blocks NLRP3 activation through nitric oxide production or IL-10 transcription, while P2X7 inhibitors prevent ATP-induced NLRP3 activation [160]. An alternative approach involves blocking signaling pathways following NLRP3 inflammasome activation, such as exploring the effects of caspase-1 inhibitors, IL-1β inhibitors, and anti-IL-18 in ongoing clinical trials for various diseases. While GSDMD is a promising execution molecule, there is limited research on molecular targeting in this area. A single prior research study showed that necrotic sulfonamide, an anti-necrotic compound, effectively decreased pyroptosis by directly interacting with GSDMD and preventing pore formation in the cell membranes of septic mice [161]. Further evaluation is necessary to determine the potential impact of GSDMD inhibitors in treating various liver conditions in the future [162]. Thus, inhibition of the process of pyroptosis should be carefully considered in the near future and more studies are needed to assess its therapeutic implications in liver disease.

5. Summary and future prospects

Pyroptosis can be likened to a double-edged weapon. Inflammatory substances released during pyroptosis not only boost the immune system's defense against pathogens, but also hinder the growth and movement of liver cancer cells through the induction of pyroptosis. However, over-activated pyroptosis can exacerbate the inflammatory response, leading to liver injury and even to the progression of liver fibrosis and hepatocellular carcinoma. Up to now, there have been two categories of pyroptosis signaling routes: traditional caspase-1-dependent and alternative caspase-4/5/11-mediated pathways. The recent research findings indicate that pyroptosis has varying impacts on the progression of viral hepatitis, ALD, MAFLD, liver fibrosis, PLC, HIRI, AIH, and sepsis-related liver damage. Despite growing insights, the molecular underpinnings of pyroptosis in liver diseases necessitate further elucidation. The NLRP3 inflammasome is a central player in liver diseases. Its activation is observed in both ALD and MAFLD, indicating a shared inflammatory mechanism [163]. However, the triggers and the subsequent inflammatory cascades differ. In MAFLD, saturated fatty acids activate NLRP3, leading to hepatocyte pyroptosis and potentially MASH, whereas in ALD, alcohol-induced damage is implicated, but the pathway to pyroptosis may involve both caspase-1 dependent and independent mechanisms. Moreover, the importance of cell-specific inflammasome activation is highlighted, with hepatocytes, Kupffer cells, and HSCs all playing distinct roles in the inflammatory response and fibrosis [164,165]. Hepatocyte pyroptosis is associated with steatosis in MAFLD, while Kupffer cell activation is crucial for the inflammatory response in MASH, and HSC activation promotes liver fibrosis [166]. Other potential mechanisms such as live fibrosis and Gut-Liver Axis have also been demonstrated, pyroptosis is implicated in liver fibrosis through different mechanisms. In MAFLD/MASH, hepatocyte pyroptosis leads to HSC activation and fibrosis, whereas in AILDs, the link to fibrosis is established but the pathway is less defined. Besides, the connection between the gut-liver axis and liver diseases is increasingly recognized, especially in primary biliary cholangitis and primary sclerosing cholangitis, where NLRP3 inflammasome activation is associated with liver injury and intestinal barrier disruption [167]. Further research is needed to explore this relationship in other liver diseases.

Our future outlook involves a concerted effort to explore the therapeutic potential of modulating pyroptosis, including the discovery of novel biomarkers and the design of targeted interventions that can mitigate liver injury and halt disease progression. By fostering a deeper understanding of pyroptosis's molecular mechanisms, we hope to contribute to the development of preventive and treatment strategies that are both effective and sustainable in the coming years.

6. Ethics approval and consent to participate

There is no human subject, and this is a review, so there is no need for ethical approval and consent.

7. Consent for publication

There are no data in this manuscript, so this is not relevant.

Author contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding statement

This review was supported by Jinhua Municipal Science and Technology Bureau Key Project (No. 2023-3-091, 2021-3-089, 2021-3-156) and Jinhua Municipal Central Hospital Science and Technology Project (No. JY2022-1-04, JY2023-1-04).

CRediT authorship contribution statement

Lujian Zhu: Writing – original draft, Funding acquisition, Conceptualization. **Hongjie Tong:** Writing – original draft. **Chao Ren:** Writing – review & editing. **Kun Chen:** Writing – review & editing. **Shengnan Luo:** Writing – review & editing. **Qin Wang:** Writing – review & editing. **Maodong Guo:** Writing – review & editing. **Yichen Xu:** Writing – review & editing. **Minli Hu:** Writing – review & editing. **Jinyong Fang:** Writing – review & editing. **Jinxian Xu:** Writing – review & editing. **Peifei Shi:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

There are no data and no material associated with this manuscript.

References

[1] S. Johannes, K. Lydia, L. Theresa, B. Sascha, H. Bernhard, "We've got to get out"-Strategies of human pathogenic fungi to escape from phagocytes, Mol. Microbiol. 121 (2023).
[2] B. Sammy, J.H. Marco, S. Andreas, Emerging connectivity of programmed cell death pathways and its physiological implications, Nat. Rev. Mol. Cell Biol. 21 (2020).
[3] L. Luobin, L. Huaqin, Z. Qinzhou, H. Jiaxuan, W. Wenmei, Research progress on the regulation of autophagy and apoptosis in insects by sterol hormone 20-hydroxyecdysone, Insects (2023) 14.
[4] Z. Qifan, Z. Min, B. Arjun, K. Rajendra, K. Thirumala-Devi, Gasdermin D promotes AIM2 inflammasome activation and is required for host protection against francisella novicida, J. Immunol. 201 (2018).
[5] X. Xiaojing, W. Xin, Z. Yi, J. Jinqing, H. Jianhe, What role does pyroptosis play in microbial infection? J. Cell Physiol. 234 (2018).
[6] M. Alireza, D.G. Alessia, C. Rocco, A. Marta, D.M. Luca, M. Wassim, High-grade infection after branched endovascular aortic repair in patient with recent COVID-19 hospitalization, Diagnostics (Basel) 14 (2024).
[7] G. Susanne, L. Aleksandra, A. Fernando, K. Benedikt, D.J. Casey, A.A. Leon, et al., Hepatocyte pyroptosis and release of inflammasome particles induce stellate cell activation and liver fibrosis, J. Hepatol. 74 (2020).
[8] W. Congqing, L. Wei, Z. Yan, Z. Guoying, S. Xuyan, H. Yohei, et al., Inflammasome activation triggers blood clotting and host death through pyroptosis, Immunity 50 (2019).
[9] F. Jianing, W. Hao, Structural mechanisms of NLRP3 inflammasome assembly and activation, Annu. Rev. Immunol. 41 (2023).
[10] K. Nathan, J. Devon, D. Yanhui, H. Yuan, The NLRP3 inflammasome: an overview of mechanisms of activation and regulation, Int. J. Mol. Sci. 20 (2019).
[11] S. Yu-Qing, L. Yan, H. Shu-Jing, L. Yan-Ting, R. Jing, Y. Fang-Fang, et al., Pyroptosis is involved in maternal nicotine exposure-induced metabolic associated fatty liver disease progression in offspring mice, Mol. Reprod. Dev. (2023).
[12] R. Sacha, G. Thomas, B. Aude, F. Alain, B. Emiliano, V. Tatiana, et al., Influence of inflammasome pathway activation in macrophages on the matrix metalloproteinase expression of human hepatic stellate cells, Int. Immunopharmacol. 72 (2019).
[13] L. Wenji, P. Jie, W. Yixin, Y. Zuxiang, Z. Zhen, W. Rui, et al., Immune and inflammatory mechanisms and therapeutic targets of gout: an update, Int. Immunopharmacol. 121 (2023).
[14] R.T. Alan, E.B. Karin, Inflammasomes and atherosclerosis: a mixed picture, Circ. Res. 132 (2023).
[15] Z. Wanxin, Z. Lei, Z. Yi, L. Bingyu, M. Chunhong, Z. Wei, et al., USP3 deubiquitinates and stabilizes the adapter protein ASC to regulate inflammasome activation, Cell Mol. Immunol. 19 (2022).
[16] T. Shaokai, G. Yuanwen, W. Yawei, L. Qinqin, Y. Yirong, L. Hao, The roles of ubiquitination and deubiquitination of NLRP3 inflammasome in inflammation-related diseases: a review, Biomol. Biomed. (2024).
[17] X. Le, M. Venkat Giri, W. Hao, Cryo-EM structures of the active NLRP3 inflammasome disc, Nature 613 (2022).
[18] P. Alessandra, C. Valeria, M. Nicolò, Z. Changqing, F. Stefano, A. Fernanda, et al., Altered inflammasome machinery as a key player in the perpetuation of Rett syndrome oxinflammation, Redox. Biol. (2019) 28.
[19] C. Ruochan, Z. Ling, Z. Shan, L. Jiao, J.Z. Herbert, K. Guido, et al., cAMP metabolism controls caspase-11 inflammasome activation and pyroptosis in sepsis, Sci. Adv. (2019) 5.
[20] S. Bahare, B. Monica, C. Mihaela, S. Ioan, V. Sanja, K. Dusanka, et al., Chronic pelvic pain syndrome: highlighting medicinal plants toward biomolecules discovery for upcoming drugs formulation, Phytother. Res. (2019) 34.
[21] M.A. Mohammed, Q. Cristina, H.-B. Jesús, S.-R. Javad, T. Sena, A. Elif Feyza, et al., A review of recent studies on the antioxidant and anti-infectious properties of senna plants, Oxid. Med. Cell Longev. (2022).
[22] B. Monica, S. Ioan, S. Ionel, Spectrophotometric and chromatographic strategies for exploring of the nanostructure pharmaceutical formulations which contains testosterone undecanoate, Sci. Rep. (2020) 10.
[23] P. Salomeia, C. Angela, B. Monica, Study on the stability and antioxidant effect of the Allium ursinum watery extract, Chem. Cent. J. 7 (2013).
[24] R.K. Sannula, M. Subbarao, K. Thirumala-Devi, Caspases in cell death, inflammation, and pyropt osis, Annu. Rev. Immunol. (2020) 38.
[25] V.O. Nina, L. Mohamed, Caspases in cell death, inflammation, and disease, Immunity 50 (2019).
[26] R. Zhiping, Z. Yutong, Y. Peng, C. Zhuang, X. Yuqiong, Q. Chaoqiang, et al., Pyroptosis in inflammatory diseases and cancer, Theranostics 12 (2022).
[27] N. Kim, S. Andreas, K. Nobuhiko, M.D. Vishva, Cell death, Cell (2024).
[28] E.B. Brandon, N.E. Ashley, Z. Hua, W. Shanzhi, Gasdermin D in pyroptosis, Acta Pharm. Sin. B (2021) 11.
[29] H. Junwei, H. Jung-Mao, H. Mien-Chie, Molecular mechanisms and functions of pyroptosis in inflammation and antitumor immunity, Mol. Cell 81 (2021).
[30] S. Gabriel, Approaching neutrophil pyroptosis, J. Mol. Biol. (2021) 434.
[31] Z. Zeqing, Y. Fangyuan, X. Wenchao, H. Jiaochan, L. Guihu, L. Yehao, et al., Attenuation of rheumatoid arthritis through the inhibition of tumor necrosis factor-induced caspase 3/gasdermin E-mediated pyroptosis, Arthrit. Rheumatol. 74 (2021).
[32] M. Magdalena, S. Mariia, B. Małgorzata, The dance of macrophage death: the interplay between the inevitable and the microenvironment, Front Immunol. (2024) 15.
[33] M. Fabio, B. Kimberly, T. Jürg, The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta, Mol. Cell 10 (2002).
[34] W. Chun, Y. Tong, X. Jianqiu, X. Canxin, A. Yael, S. Kai, et al., NLRP3 inflammasome activation triggers gasdermin D-independent inflammation, Sci. Immunol. (2021) 6.
[35] H. Yuan, H. Hideki, N. Gabriel, Mechanism and regulation of NLRP3 inflammasome activation, Trends Biochem. Sci. 41 (2016).
[36] Y. Xinru, L. Guangzhong, H. Zhifu, C. Jijie, Structural biology of NOD-Like receptors, Adv. Exp. Med. Biol. 1172 (2019).
[37] L. Gilyoung, A. Huijeong, L. Eunsong, L. Geun-Shik, The role of NLRP3 inflammasomes in trained immunity, Front. Biosci. (Landmark Ed.) 28 (2023).
[38] M.P. Jaye, A.M. Daniel, NOD-like receptors and inflammasomes: a review of their canonical and non-canonical signaling pathways, Arch. Biochem. Biophys. (2019) 670.
[39] P. Virginie, D. Catherine, A.M. Daniel, T. Jürg, The inflammasome: a danger sensing complex triggering innate immunity, Curr. Opin. Immunol. 19 (2007).
[40] X. Jie, N. Gabriel, The NLRP3 inflammasome: activation and regulation, Trends Biochem. Sci. 48 (2022).
[41] C. Jian-Zhou, C. Zhi Huan, H.K.L. Lina, New insights into nucleic acid sensor AIM2: the potential benefit in targeted therapy for cancer, Pharmacol. Res. 200 (2024).
[42] A.M. Edward, E.W. Sarah, Innate immune detection of bacterial virulence factors via the NLRC4 inflammasome, J. Clin. Immunol. 30 (2010).
[43] M. Si Ming, K. Thirumala-Devi, Regulation of inflammasome activation, Immunol. Rev. (2015) 265.
[44] L. Zhe, G. Jialong, B. Liqi, Role of the NLRP3 inflammasome in autoimmune diseases, Biomed. Pharmacother. 130 (2020).
[45] M. Ankit, K. Thirumala-Devi, Inflammasome activation and assembly at a glance, J. Cell Sci. 130 (2017).
[46] P.A. William, P. Gaby, G. Cem, IL-1, IL-18, and IL-33 families of cytokines, Immunol. Rev. 223 (2008).
[47] D. Jian, Y. Xiao-Qiang, W. Pei-Hui, Inflammasome activation and Th17 responses, Mol. Immunol. 107 (2019).
[48] W. Chengbin, Y. Hua, B. Sahana, M. Renee, M. Limary, S. Ling, et al., Molecular construction and optimization of anti-human IL-1alpha/beta dual variable domain immunoglobulin (DVD-Ig) molecules, MAbs 1 (2010).
[49] H. Yasuaki, N. Yuji, Interleukin-18 in Inflammatory Kidney Disease. Front Med (Lausanne) 8 (2021).
[50] A. Akira, N. Atsushi, Pro- and anti-inflammatory roles of interleukin (IL)-33, IL-36, and IL-38 in inflammatory bowel disease, J. Gastroenterol. 58 (2022).
[51] L. Emma, R. Stephane, G. Violette, A. G-d-P, M. Bernard, G. Jean-Philippe, et al., IL-33 is processed into mature bioactive forms by neutrophil elastase and cathepsin G, Proc. Natl. Acad. Sci. U.S.A. 109 (2012).
[52] S.Y. Amir, G. Kamran, The interleukin-1 family, Adv. Exp. Med. Biol. 941 (2016).
[53] H. Claire, O. Antoni, L. Stuart, M.-R. Kelly, C. Shamshad, L.-M. Gerald, et al., NLRP3 inflammasome priming and activation are regulated by a phosphatidylinositol-dependent mechanism, Immunohorizons 6 (2022).
[54] H. Alexander, A. Stefano, H. Svenja, E.C. Sarah, C.R. Marah, L. Chris, et al., The immunomodulatory metabolite itaconate modifies NLRP3 and inhibits inflammasome activation, Cell Metab. 32 (2020).
[55] Z. Wen-Juan, C. Shu-Juan, Z. Shun-Chang, W. Su-Zhen, W. Hui, Inflammasomes and fibrosis, Front Immunol (2021) 12.
[56] C.B. Katherine, L. Sirui, L. Kaixin, P.-Y.-T. Jenny, A 360° view of the inflammasome: Mechanisms of activation, cell death, and diseases, Cell 186 (2023).
[57] F. Xuhui, W. Yanshi, Z. Yu, L. Yelin, K.-K. Joanne, W. Li, NLRP3 inflammasome and its critical role in gynecological disorders and obstetrical complications, Front Immunol. 11 (2021).
[58] L. Liang, T. Wei, Y. Fan, Role of inflammasome in chronic kidney disease, Adv. Exp. Med. Biol. 1165 (2019).
[59] S.R. Kim, T. Gee Ann, R. Pritisha, C. Rae, B. Stefan, S. Zijin, et al., ZAKα-driven ribotoxic stress response activates the human NLRP1 inflammasome, Science 377 (2022).
[60] H. Yuan, Y.Z. Melody, Y. Dahai, M. Benny, N. Gabriel, NEK7 is an essential mediator of NLRP3 activation downstream of potassium efflux, Nature 530 (2016).
[61] L.-O.-H. Elizabeth, H. Hsin-Che, D.R. Sahana, W. Qinghui, C. Qifeng, M.O. M. Claire, et al., Protein folding stress potentiates NLRP1 and CARD8 inflammasome activation, Cell Rep. 42 (2023).
[62] V.H. Filip, V.O. Nina, V.G. Hanne, D.V. Nathalia, V.L. Geert, V. Peter, et al., Bacillus anthracis induces NLRP3 inflammasome activation and caspase-8-mediated apoptosis of macrophages to promote lethal anthrax, Proc. Natl. Acad. Sci. U.S.A. 119 (2022).
[63] Y. Xiaowei, Z. Lan, L. Wanlu, T. Xuelian, Y. Junli, W. Puyu, et al., The effect of NLRP inflammasome on the regulation of AGEs-induced inflammatory response in human periodontal ligament cells, J. Periodontal. Res. 54 (2019).

[64] R. Pritisha, P. Miriam, G. Leana, V. Anna Constance, S.R. Kim, T. Gee Ann, et al., Mechanistic basis for potassium efflux-driven activation of the human NLRP1 inflammasome, Proc. Natl. Acad. Sci. U.S.A. 121 (2024).
[65] S. Ao-Qi, G. Bo, F. Jun-Juan, Z. Ya-Jing, Z. Jun, W. Yu-Ling, et al., NLRP1 inflammasome contributes to chronic stress-induced depressive-like behaviors in mice, J. Neuroinflam. 17 (2020).
[66] H. Yi, X. Wen, Z. Rongbin, NLRP3 inflammasome activation and cell death, Cell Mol. Immunol. 18 (2021).
[67] Z. Xiaoyan, L. Qiang, X. Guang, X. Xiaohe, B. Zhaofang, The mechanism of NLRP3 inflammasome activation and its pharmacological inhibitors, Front Immunol. 13 (2023).
[68] G.B. Franz, H. Gabor, S. Andrea, S.A. Emad, M. Kelly, S. David, et al., Cutting edge: NF-kappaB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression, J. Immunol. 183 (2009).
[69] X. Rong, Y. Li-Sha, G. Ying-Qing, L. Na, L. Ya-Ping, Z. Zhi-Ya, et al., Extracellular ATP contributes to the reactive oxygen species burst and exaggerated mitochondrial damage in D-galactosamine and lipopolysaccharide-induced fulminant hepatitis, Int. Immunopharmacol. 130 (2024).
[70] T. Kohei, J. Tatsunori, N. Daiki, K. Hachiro, P. Jeong Hoon, Y. Shin-Ichiro, et al., The lysosomal Ragulator complex activates NLRP3 inflammasome in vivo via HDAC6, EMBO J. 42 (2022).
[71] D. Abishai, L. Nhat-Tu, T. Masafumi, Loop between NLRP3 inflammasome and reactive oxygen species, Antioxid Redox Signal 36 (2021).
[72] W. Fenghong, L. Qingqing, M. Yuexiao, S. Mengqi, L. Tianyu, L. Lisen, et al., Silica nanoparticles induce pyroptosis and cardiac hypertrophy via ROS/NLRP3/Caspase-1 pathway, Free Radic. Biol. Med. 182 (2022).
[73] P. Meng-Ling, F. Yu, W. Chu-Wen, Z. Ying, R. Hang, Z. Shan-Shan, Signaling pathways related to oxidative stress in diabetic cardiomyopathy, Front Endocrinol. (Lausanne) 13 (2022).
[74] K.B. Leah, S.S. Joshua, V. Karthik, E.R. Arianne, A.P. Taylor, S. Marten, et al., Mitochondrial electron transport chain is necessary for NLRP3 inflammasome activation, Nat. Immunol. 23 (2022).
[75] B. Renate, R. Isabella, The NAIP/NLRC4 inflammasome in infection and pathology, Mol. Aspects Med. 76 (2020).
[76] B. Sundaram, T. Kanneganti, Advances in Understanding Activation and Function of the NLRC4 Inflammasome, Int. J. Mole. Sci. 22 (2021).
[77] M. Egan, J. Zhang, S. Shin, Human and mouse NAIP/NLRC4 inflammasome responses to bacterial infection, Curr. Opin. Microbiol. 73 (2023) 102298.
[78] J. Quan, F. Gao, T. Ma, W. Ye, X. Gao, M. Deng, et al., Toxoplasma gondii induces pyroptosis in human placental trophoblast and amniotic cells by inducing ROS production and activation of cathepsin B and NLRP1/NLRP3/NLRC4/AIM2 inflammasome, Am. J. Pathol. 193 (2023) 2047–2065.
[79] W. Chou, Z. Guo, H. Guo, L. Chen, G. Zhang, K. Liang, et al., AIM2 in regulatory T cells restrains autoimmune diseases, Nature 591 (2021) 300–305.
[80] V. Leal, A. Pontillo, Canonical Inflammasomes, Meth. Mole. Biol. (Clifton, NJ) 2696 (2023) 1–27.
[81] V. Hornung, A. Ablasser, M. Charrel-Dennis, F. Bauernfeind, G. Horvath, D. Caffrey, et al., AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC, Nature 458 (2009) 514–518.
[82] L. Du, X. Wang, S. Chen, X. Guo, The AIM2 inflammasome: a novel biomarker and target in cardiovascular disease, Pharmacol. Res. 186 (2022) 106533.
[83] R. Miao, C. Jiang, W. Chang, H. Zhang, J. An, F. Ho, et al., Gasdermin D permeabilization of mitochondrial inner and outer membranes accelerates and enhances pyroptosis, Immunity 56 (2023), 2523-2541.e2528.
[84] X. Shi, Q. Sun, Y. Hou, H. Zeng, Y. Cao, M. Dong, et al., Recognition and maturation of IL-18 by caspase-4 noncanonical inflammasome, Nature 624 (2023) 442–450.
[85] Y. Song, J. Song, M. Wang, J. Wang, B. Ma, W. Zhang, Porcine gasdermin D is a substrate of caspase-1 and an executioner of pyroptosis, Front. Immunol. 13 (2022) 828911.
[86] A. Balasubramanian, L. Ghimire, A. Hsu, H. Kambara, X. Liu, T. Hasegawa et al., Palmitoylation of gasdermin D directs its membrane translocation and pore formation in pyroptosis, bioRxiv : the preprint server for biology, 2023.
[87] S. Zhang, X. Guan, W. Liu, Z. Zhu, H. Jin, Y. Zhu, et al., YTHDF1 alleviates sepsis by upregulating WWP1 to induce NLRP3 ubiquitination and inhibit caspase-1-dependent pyroptosis, Cell Death Disc. 8 (2022) 244.
[88] J. Moretti, B. Jia, Z. Hutchins, S. Roy, H. Yip, J. Wu, et al., Caspase-11 interaction with NLRP3 potentiates the noncanonical activation of the NLRP3 inflammasome, Nat. Immunol. 23 (2022) 705–717.
[89] F. Zhu, J. Ma, W. Li, Q. Liu, X. Qin, Y. Qian, et al., The orphan receptor Nur77 binds cytoplasmic LPS to activate the non-canonical NLRP3 inflammasome, Immunity 56 (2023), 753-767.e758.
[90] C. Sandall, B. Ziehr, J. MacDonald, ATP-binding and hydrolysis in inflammasome activation, Molecules (Basel, Switzerland) 25 (2020).
[91] M. Bosso, F. Kirchhoff, Emerging role of PYHIN proteins as antiviral restriction factors, Viruses 12 (2020).
[92] D. Feng, L. Guo, J. Liu, Y. Song, X. Ma, H. Hu, et al., DDX3X deficiency alleviates LPS-induced H9c2 cardiomyocytes pyroptosis by suppressing activation of NLRP3 inflammasome, Exp. Ther. Med. 22 (2021) 1389.
[93] J. Li, C. Ma, D. Di, A narrative review of pyrolysis and its role in ulcerative colitis, Euro. Rev. Med. Pharmacol. Sci. 26 (2022) 1156–1163.
[94] Z. Wang, W. Chan, Y. Yue, A significant other: Non-canonical caspase-4/5/11 inflammasome in periodontitis, Oral Dis. 29 (2023) 1927–1936.
[95] J. An, S. Kim, D. Hwang, K. Lee, M. Kim, E. Yang, et al., Caspase-4 disaggregates lipopolysaccharide micelles via LPS-CARD interaction, Sci. Rep. 9 (2019) 826.
[96] T. Luo, X. Zhou, M. Qin, Y. Lin, J. Lin, G. Chen, et al., Corilagin restrains NLRP3 inflammasome activation and pyroptosis through the ROS/TXNIP/NLRP3 pathway to prevent inflammation, Oxid. Med. Cell. Longev. 2022 (2022) 1652244.
[97] V. Šmíd, Liver tests, Casop. Lekaru Cesk. 161 (2022) 52–56.
[98] Q. Chu, Y. Jiang, W. Zhang, C. Xu, W. Du, G. Tuguzbaeva, et al., Pyroptosis is involved in the pathogenesis of human hepatocellular carcinoma, Oncotarget 7 (2016) 84658–84665.
[99] Y. Yang, S. Kim, E. Seki, Inflammation and liver cancer: molecular mechanisms and therapeutic targets, Semin. Liver Dis. 39 (2019) 26–42.
[100] Y. Xiao, H. Zhang, Q. Ma, R. Huang, J. Lu, X. Liang, et al., YAP1-mediated pancreatic stellate cell activation inhibits pancreatic cancer cell proliferation, Cancer Lett. 462 (2019) 51–60.
[101] J. Chen, V. Deshpande, IgG4-related disease and the liver, Gastroenterol. Clin. North Am. 46 (2017) 195–216.
[102] M. Odenwald, S. Paul, Viral hepatitis: past, present, and future, World J. Gastroenterol. 28 (2022) 1405–1429.
[103] Teschke R. Aluminum, Arsenic, beryllium, cadmium, chromium, cobalt, copper, iron, lead, mercury, molybdenum, nickel, platinum, thallium, titanium, vanadium, and zinc: molecular aspects in experimental liver injury, Int. J. Mole. Sci. 23 (2022).
[104] U. Ohto, Activation and regulation mechanisms of NOD-like receptors based on structural biology, Front. Immunol. 13 (2022) 953530.
[105] T. Khaliullin, E. Kisin, N. Yanamala, S. Guppi, M. Harper, T. Lee, et al., Comparative cytotoxicity of respirable surface-treated/untreated calcium carbonate rock dust particles in vitro, Toxicol. Appl. Pharmacol. 362 (2019) 67–76.
[106] S. Yu, X. Ren, F. Meng, X. Guo, J. Tao, W. Zhang, et al., TIM3/CEACAM1 pathway involves in myeloid-derived suppressor cells induced CD8 T cells exhaustion and bone marrow inflammatory microenvironment in myelodysplastic syndrome, Immunology 168 (2023) 273–289.
[107] X. Ding, Q. Lei, T. Li, L. Li, B. Qin, Hepatitis B core antigen can regulate NLRP3 inflammasome pathway in HepG2 cells, J. Med. Virol. 91 (2019) 1528–1536.
[108] Y. Mou, Y. Ma, X. Yuan, M. Wang, Y. Liu, C. Pei, et al., viaCystathionine β-synthase suppresses NLRP3 inflammasome activation redox regulation in microglia, Antioxid. Redox Signal. (2023).
[109] W. Xie, J. Ding, X. Xie, X. Yang, X. Wu, Z. Chen, et al., Hepatitis B virus X protein promotes liver cell pyroptosis under oxidative stress through NLRP3 inflammasome activation, Inflamm. Res.: Off. J. Euro. Histam. Res. Soc. [et Al] 69 (2020) 683–696.
[110] H. Wallace, L. Wang, C. Gardner, C. Corkum, M. Grant, K. Hirasawa, et al., Crosstalk between pyroptosis and apoptosis in hepatitis C virus-induced cell death, Front. Immunol. 13 (2022) 788138.
[111] S. McRae, J. Iqbal, M. Sarkar-Dutta, S. Lane, A. Nagaraj, N. Ali, et al., Withdrawal: the hepatitis C virus-induced NLRP3 inflammasome activates the sterol regulatory element-binding protein (SREBP) and regulates lipid metabolism, J. Biol. Chem. 293 (2018) 20011.
[112] A. Negash, R. Olson, S. Griffin, M. Gale, Modulation of calcium signaling pathway by hepatitis C virus core protein stimulates NLRP3 inflammasome activation, PLoS Pathog. 15 (2019) e1007593.
[113] J. Kai, X. Yang, Z. Wang, F. Wang, Y. Jia, S. Wang, et al., Oroxylin a promotes PGC-1α/Mfn2 signaling to attenuate hepatocyte pyroptosis via blocking mitochondrial ROS in alcoholic liver disease, Free Radic. Biol. Med. 153 (2020) 89–102.
[114] Q. Cheng, J. Pan, Z. Zhou, F. Yin, H. Xie, P. Chen, et al., Caspase-11/4 and gasdermin D-mediated pyroptosis contributes to podocyte injury in mouse diabetic nephropathy, Acta Pharmacol. Sin. 42 (2021) 954–963.
[115] J. Deng, L. Qin, S. Qin, R. Wu, G. Huang, Y. Fang, et al., NcRNA regulated pyroptosis in liver diseases and traditional chinese medicine intervention: a narrative review, J. Inflamm. Res. 17 (2024) 2073–2088.
[116] M. Meroni, M. Longo, P. Dongiovanni, Alcohol or gut microbiota: who is the guilty? Int. J. Mole. Sci. (2019) 20.
[117] S. Valles, A. Blanco, I. Azorin, R. Guasch, M. Pascual, M. Gomez-Lechon, et al., Chronic ethanol consumption enhances interleukin-1-mediated signal transduction in rat liver and in cultured hepatocytes, Alcohol. Clin. Exp. Res. 27 (2003) 1979–1986.
[118] C. McClain, D. Cohen, C. Dinarello, J. Cannon, S. Shedlofsky, A. Kaplan, Serum interleukin-1 (IL-1) activity in alcoholic hepatitis, Life Sci. 39 (1986) 1479–1485.
[119] C. Hsiang, S. Wu, S. Cheng, T. Ho, Acetaldehyde-induced interleukin-1beta and tumor necrosis factor-alpha production is inhibited by berberine through nuclear factor-kappaB signaling pathway in HepG2 cells, J. Biomed. Sci. 12 (2005) 791–801.
[120] K. Holloway, J. Douglas, T. Rafferty, C. Kane, P. Drew, Ethanol induces neuroinflammation in a chronic plus binge mouse model of alcohol use disorder via TLR4 and MyD88-dependent signaling, Cells 12 (2023).
[121] G. Zhong, G. Rao, L. Tang, S. Wu, Z. Tang, R. Huang, et al., Combined effect of arsenic and polystyrene-nanoplastics at environmentally relevant concentrations in mice liver: activation of apoptosis, pyroptosis and excessive autophagy, Chemosphere 300 (2022) 134566.
[122] W. Liu, X. Han, Q. Li, L. Sun, J. Wang, Iguratimod ameliorates bleomycin-induced pulmonary fibrosis by inhibiting the EMT process and NLRP3 inflammasome activation, Biomed. Pharmacother. = Biomed. Pharmacother. 153 (2022) 113460.
[123] J. Zhang, M. Li, S. Lin, Y. Cheng, J. Fan, Y. Chen, Therapeutic effect of prolyl endopeptidase inhibitor in high-fat diet-induced metabolic dysfunction-associated fatty liver disease, J. Clin. Transl. Hepatol. 11 (2023) 1035–1049.

[124] N. Zhang, X. Liu, L. Xie, X. Shen, J. Wu, Impaired mitophagy triggers NLRP3 inflammasome activation during the progression from nonalcoholic fatty liver to nonalcoholic steatohepatitis, Lab. Invest.; J. Tech. Methods Pathol. 99 (2019) 749–763.
[125] J. Liu, T. Wang, K. He, M. Xu, J. Gong, Cardiolipin inhibitor ameliorates the non-alcoholic steatohepatitis through suppressing NLRP3 inflammasome activation, Eur. Rev. Med. Pharmacol. Sci. 23 (2019) 8158–8167.
[126] D. Gabbia, K. Sayaf, I. Zanotto, M. Colognesi, Y. Frion-Herrera, M. Carrara, et al., Tyrosol attenuates NASH features by reprogramming the hepatic immune milieu, Eur. J. Pharmacol. 969 (2024) 176453.
[127] H. Mitsuyoshi, K. Yasui, T. Hara, H. Taketani, H. Ishiba, A. Okajima, et al., Hepatic nucleotide binding oligomerization domain-like receptors pyrin domain-containing 3 inflammasomes are associated with the histologic severity of non-alcoholic fatty liver disease, Hepatol. Res.: Off. J. Japan Soc. Hepatol. 47 (2017) 1459–1468.
[128] M. Flisiak-Jackiewicz, D. Lebensztejn, Update on pathogenesis, diagnostics and therapy of nonalcoholic fatty liver disease in children, Clin. Experim. Hepatol. 5 (2019) 11–21.
[129] L. Campana, H. Esser, M. Huch, S. Forbes, Liver regeneration and inflammation: from fundamental science to clinical applications, Nat. Rev. Mol. Cell Biol. 22 (2021) 608–624.
[130] V. Kumar, X. Xin, J. Ma, C. Tan, N. Osna, R. Mahato, Therapeutic targets, novel drugs, and delivery systems for diabetes associated NAFLD and liver fibrosis, Adv. Drug Deliv. Rev. 176 (2021) 113888.
[131] E. Ramos-Tovar, P. Muriel, NLRP3 inflammasome in hepatic diseases: a pharmacological target, Biochem. Pharmacol. 217 (2023) 115861.
[132] R. Li, J. Wang, R. Li, F. Zhu, W. Xu, G. Zha, et al., ATP/P2X7-NLRP3 axis of dendritic cells participates in the regulation of airway inflammation and hyper-responsiveness in asthma by mediating HMGB1 expression and secretion, Exp. Cell Res. 366 (2018) 1–15.
[133] E. Leiva-Salcedo, C. Coddou, F. Rodríguez, A. Penna, X. Lopez, T. Neira, et al., Lipopolysaccharide inhibits the channel activity of the P2X7 receptor, Mediat. Inflamm. 2011 (2011) 152625.
[134] X. Liu, S. Xia, Z. Zhang, H. Wu, J. Lieberman, Channelling inflammation: gasdermins in physiology and disease, Nat. Rev. Drug Discov. 20 (2021) 384–405.
[135] M. Deng, S. Sun, R. Zhao, R. Guan, Z. Zhang, S. Li, et al., The pyroptosis-related gene signature predicts prognosis and indicates immune activity in hepatocellular carcinoma, Mole. Med. (Cambridge, Mass) 28 (2022) 16.
[136] Q. Wei, P. Guo, K. Mu, Y. Zhang, W. Zhao, W. Huai, et al., Estrogen suppresses hepatocellular carcinoma cells through ERβ-mediated upregulation of the NLRP3 inflammasome, Lab. Invest.; J. Tech. Meth. Pathol. 95 (2015) 804–816.
[137] J. Shi, Y. Zhao, K. Wang, X. Shi, Y. Wang, H. Huang, et al., Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death, Nature 526 (2015) 660–665.
[138] W. Lin, Z. Zhao, Z. Ni, Y. Zhao, W. Du, S. Chen, IFI16 restoration in hepatocellular carcinoma induces tumour inhibition via activation of p53 signals and inflammasome, Cell Prolifer. 50 (2017).
[139] Y. Zhang, N. Ding, Y. Zeng, Y. Xiang, M. Yang, F. Hong, et al., New progress in roles of nitric oxide during hepatic ischemia reperfusion injury, World J. Gastroenterol. 23 (2017) 2505–2510.
[140] T. Luangmonkong, S. Suriguga, H. Mutsaers, G. Groothuis, P. Olinga, M. Boersema, Targeting oxidative stress for the treatment of liver fibrosis, Rev. Physiol. Biochem. Pharmacol. 175 (2018) 71–102.
[141] Q. Zhang, J. Wei, Z. Liu, X. Huang, M. Sun, W. Lai, et al., STING signaling sensing of DRP1-dependent mtDNA release in kupffer cells contributes to lipopolysaccharide-induced liver injury in mice, Redox Biol. 54 (2022) 102367.
[142] K. Jia, Y. Zhang, R. Luo, R. Liu, Y. Li, J. Wu, et al., viaActeoside ameliorates hepatic ischemia-reperfusion injury reversing the senescent fate of liver sinusoidal endothelial cells and restoring compromised sinusoidal networks, Int. J. Biol. Sci. 19 (2023) 4967–4988.
[143] L. Lu, Z. Wang, H. Zhang, T. Liu, H. Fang, Drynaria fortunei improves lipid profiles of elderly patients with postmenopausal osteoporosis regulation of Notch1-NLRP3 inflammasome-mediated inflammation, Gynecol. Endocrinol.: Off. J. Int. Soc. Gynecol. Endocrinol. 38 (2022) 176–180.
[144] A. Rauf, M. Shah, D. Yellon, S. Davidson, Role of caspase 1 in ischemia/reperfusion injury of the myocardium, J. Cardiovasc. Pharmacol. 74 (2019) 194–200.
[145] P. Pan, M. Shen, Z. Yu, W. Ge, K. Chen, M. Tian, et al., SARS-CoV-2 N protein promotes NLRP3 inflammasome activation to induce hyperinflammation, Nat. Commun. 12 (2021) 4664.
[146] B. Terziroli Beretta-Piccoli, G. Mieli-Vergani, D. Vergani, Autoimmmune hepatitis, Cell. Mol. Immunol. 19 (2022) 158–176.
[147] Z. Macek Jilkova, M. Hilleret, T. Gerster, N. Sturm, M. Mercey-Ressejac, J. Zarski, et al., Increased intrahepatic expression of immune checkpoint molecules in autoimmune liver disease, Cells 10 (2021).
[148] G. Webb, G. Hirschfield, P. Lane, OX40, OX40L and autoimmunity: a comprehensive review, Clin. Rev. Allerg. Immunol. 50 (2016) 312–332.
[149] J. Luan, X. Zhang, S. Wang, Y. Li, J. Fan, W. Chen, et al., NOD-Like receptor protein 3 inflammasome-dependent Il-1β accelerated ConA-induced hepatitis, Front. Immunol. 9 (2018) 758.
[150] J. Long, Y. Sun, S. Liu, S. Yang, C. Chen, Z. Zhang, et al., Targeting pyroptosis as a preventive and therapeutic approach for stroke, Cell Death Disc. 9 (2023) 155.
[151] K. Wang, W. Wu, X. Jiang, J. Xia, L. Lv, S. Li, et al., Multi-omics analysis reveals the protection of gasdermin d in concanavalin a-induced autoimmune hepatitis, Microbiol. Spect. 10 (2022) e0171722.
[152] M. Feng, Y. Yu, Y. Chen, X. Yang, B. Li, W. Jiang, HBx-induced PLAR overexpression mediates podocyte pyroptosis through the ROS-NLRP3 signaling pathway, Ren. Fail. 45 (2023) 2170808.
[153] Y. Li, H. Zhang, C. Chen, K. Qiao, Z. Li, J. Han, et al., Biomimetic immunosuppressive exosomes that inhibit cytokine storms contribute to the alleviation of sepsis, Adv. Mater. (Deerfield Beach, Fla) 34 (2022) e2108476.
[154] S. Liang, M. Xing, X. Chen, J. Peng, Z. Song, W. Zou, Predicting the prognosis in patients with sepsis by a pyroptosis-related gene signature, Front. Immunol. 13 (2022) 1110602.
[155] Z. Li, T. Liu, Y. Feng, Y. Tong, Y. Jia, C. Wang, et al., γPPAR alleviates sepsis-induced liver injury by inhibiting hepatocyte pyroptosis via inhibition of the ROS/TXNIP/NLRP3 signaling pathway, Oxid. Med. Cell. Longev. 2022 (2022) 1269747.
[156] B. Sen, A. Rastogi, R. Nath, S. Shasthry, V. Pamecha, S. Pandey, et al., Senescent hepatocytes in decompensated liver show reduced UPR and its key player, CLPP, attenuates senescence in vitro, Cell. Mol. Gastroenterol. Hepatol. 8 (2019) 73–94.
[157] D. Nguyen, Y. Jin, T. Nguyen, L. Kim, K. Heo, 3'-Sialyllactose protects against LPS-induced endothelial dysfunction by inhibiting superoxide-mediated ERK1/2/STAT1 activation and HMGB1/RAGE axis, Life Sci. 338 (2024) 122410.
[158] R. Yang, X. Zhang, A potential new pathway for heparin treatment of sepsis-induced lung injury: inhibition of pulmonary endothelial cell pyroptosis by blocking hMGB1-LPS-induced caspase-11 activation, Front. Cell. Infect. Microbiol. 12 (2022) 984835.
[159] J. Qu, Z. Yuan, G. Wang, X. Wang, K. Li, The selective NLRP3 inflammasome inhibitor MCC950 alleviates cholestatic liver injury and fibrosis in mice, Int. Immunopharmacol. 70 (2019) 147–155.
[160] N. Kopitar-Jerala, The role of interferons in inflammation and inflammasome activation, Front. Immunol. 8 (2017) 873.
[161] Y. Guo, J. Ren, H. Liu, T. Li, S. Zhang, H. Wang, [Effects of MCC950 on nerve injury in rats with intracerebral hemorrhage], Zhongguo ying yong sheng li xue za zhi = Zhongguo yingyong shenglixue zazhi = Chin. J. Appl. Physiol. 38 (2022) 11–16.
[162] J. Rathkey, J. Zhao, Z. Liu, Y. Chen, J. Yang, H. Kondolf, et al., Chemical disruption of the pyroptotic pore-forming protein gasdermin D inhibits inflammatory cell death and sepsis, Sci. Immunol. 3 (2018).
[163] J. Wu, S. Lin, B. Wan, B. Velani, Y. Zhu, Pyroptosis in liver disease: new insights into disease mechanisms, Aging Dis. 10 (2019) 1094–1108.
[164] J. Wang, Z. Sun, J. Xie, W. Ji, Y. Cui, Z. Ai, et al., Inflammasome and pyroptosis in autoimmune liver diseases, Front. Immunol. 14 (2023) 1150879.
[165] R.M. de Carvalho, G. Szabo, Role of the inflammasome in liver disease, Annu. Rev. Pathol. 17 (2022) 345–365.
[166] C. Gan, Q. Cai, C. Tang, J. Gao, Inflammasomes and Pyroptosis of Liver Cells in Liver Fibrosis, Front. Immunol. 13 (2022) 896473.
[167] C. Hsu, B. Schnabl, The gut-liver axis and gut microbiota in health and liver disease, Nat. Rev. Microbiol. 21 (2023) 719–733.